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A Stochastic Approach to Nonlinear Mixed Effects Modeling: Applications to Pharmacokinetics Modeling of Metformin

Hien Tran

North Carolina State University

tran@math.ncsu.edu

Abstract: Nonlinear mixed effects modeling (NLME) is a common and powerful methodology for analyzing repeated measures to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) properties of a drug. Within this modeling framework, the variability is decomposed into inter-individual and intra-individual variability. The inter-individual variability accounts for factors that facilitate heterogeneity of subjects within the population. The intra-individual (residual) variability is not only associated with the errors due to measurement collection such as assay sensitivity, dosing, and sampling, but also with errors due to model misspecification, approximations due to model evaluation, and model parameters. Utilizing stochastic differential equations (SDE) within the NLME framework allows the decoupling of the measurement errors from the model misspecification. This leads the SDE approach to be a novel tool for model refinement. Using Metformin clinical pharmacokinetic (PK) data, the process of model development through the use of SDEs in population PK modeling was done to study the dynamics of absorption rate. A base model was constructed and then refined by using the system noise terms of the SDEs to track model parameters and model misspecification. This article focuses on implementing the extended Kalman filter (EKF) and unscented Kalman filter (UKF) in an NLME framework for parameter estimation and model development, comparing the methodologies as well as illustrating their difficulties. The Kalman filter algorithms were successfully implemented in NLME models for population pharmacokinetic analysis, and highlighted the application of SDEs and their uses in model development and refinement. It also indicated the difficulties that may be encountered when using these methodologies.